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EXAMINER	
JOYCE, CATHERINE	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,307	HU ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *11,16-18,21-26 and 29-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-15,19,20,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-61 are pending, and claims 11, 16-18, 21-26, and 29-61 are withdrawn from consideration as drawn to a non-elected invention

2. Claim 1-10, 12-15, 19, 20, 27 and 28 are under examination.

3. Applicant's election without traverse of the invention of Group I, and of the species of a method step sequence of "contacting the tumor cells with a lytic agent before applying the in vivo stimulus", "nasopharyngeal carcinoma", "oncolytic virus", "adenovirus", "p53" as the gene product lacking in tumor cells, "p53" as the viral oncoprotein, "SEQ ID NO:1", "a cytolytic gene", "local hyperthermia", and HSP-70, in the reply filed on December 1, 2006 is acknowledged.

Applicant's indication that the reference to "local hypothermia" rather than "local hyperthermia" in the restriction requirement might be an error is appreciated. Indeed, the reference to "local hypothermia" rather than "local hyperthermia" in the restriction requirement was an error and "local hyperthermia" was intended.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10, 12-15, 19, 20, 27 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are objected to because claim 1 does not contain a step that relates the method steps back to the preamble.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 15 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are drawn to a method for ablating tumor cells in a subject having at least one tumor site, the method comprising (a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor and (b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor, wherein the lytic agent comprises an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1 and the lytic conditions comprise infective conditions.

Although drawn to the DNA arts, the finding in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by

> function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although, the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at

issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1" per Lilly by structurally describing a representative number of species of "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1" or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1", in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1", nor does the specification provide any partial structure of such oncolytic viruses, nor any physical or chemical characteristics of the "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1", nor any functional characteristics coupled with a known or disclosed correlation between structure and function, other than SEQ ID NO:1 and 2. Although the specification discloses the sequences of SEQ ID NOs:1 and 2, this does not provide a description of "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1" of the claimed methods that would satisfy the standard set out in Enzo.

The specification also fails to describe the claimed "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1" by the test set out in Lilly. The specification describes only the sequences of SEQ ID NO:1 and SEQ ID NO:2. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural

features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1" or the claimed method employing "an isolated oncolytic virus having a sequence at least 95% to SEQ ID NO#1"

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ries et al. (2002, January 7, Br. J. Cancer 86(1):5-11).

The claims are drawn to the following:

a method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

wherein the lytic agent comprises an isolated oncolytic virus that replicates in the tumor cells and is inhibited from replicating in non-tumor cells; and wherein the lytic conditions comprise infective conditions **(claim 12)**,

wherein the lytic agent comprises an isolated oncolytic virus that replicates in the tumor cells and is inhibited from replicating in non-tumor cells; and wherein the lytic conditions comprise infective conditions, wherein the isolated oncolytic virus comprises an adenovirus not having a functional viral oncoprotein; and wherein tumor cells lack a functional p53- gene product **(claim 13)**,

wherein the functional viral oncoprotein comprises a p53- binding protein **(claim 14)**.

It is noted that paragraph 0057 of the specification defines "stimulus" as being "any action or agent that causes or changes an activity in an organism, organ, cell, or part thereof", wherein "[I]n general, the stimulus described in specific embodiments are "in addition" to any change or impulse resulting from the introduction of the lytic agent to the tumor cells". Thus, for examination purposes, the term "stimulus" is interpreted to encompass chemotherapeutic agents as such agents would be expected to cause or change an activity in a tumor cell.

Ries et al. teaches that ONYX-015 is an adenovirus which contains an 827 bp deletion in the E1B region of the viral genome and a point mutation that generates a stop codon preventing expression of a truncate form of the E1B55K protein (page 7). Ries et al. further teaches that tumor cells that do not possess functional p53 gene should support replication of the ONYX-015 virus and that replication of ONYX-015 should be restricted to p53 deficient cells resulting in selective destruction of cancer cells (page 7). Ries et al. further teaches that clinical studies have been conducted on cancers including head and neck cancer, pancreatic carcinoma, metastatic solid tumors, colorectal cancer liver metastases, liver metastases and ovarian cancer (Tables 1a and 1b). Ries et al. further teaches that the ONYX-015 has been administered in various treatment schedules including single intratumoral injections, repeated intratumoral injections, and repeated intravenous injections (Tables 1a and 1b), and that ONYX-015 therapy has been combined with chemotherapy (Tables 1a and 1b). Ries et al. further teaches that preclinical studies suggested a potential

synergistic effect of chemotherapy on ONYX-015 and that a phase II study to evaluate the combination in patients with recurrent head and neck cancer mirrored the preclinical data with the frequent occurrence of complete remissions (page 9). Thus, all of the claim limitations are met.

10. Claims 1, 10, 12-14, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,080,578 (issued June 2, 2000).

A method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

wherein the tumor comprises: a nasopharyngeal carcinoma **(claim 10)**,

wherein the lytic agent comprises an isolated oncolytic virus that replicates in the tumor cells and is inhibited from replicating in non-tumor cells; and wherein the lytic conditions comprise infective conditions **(claim 12)**,

wherein the lytic agent comprises an isolated oncolytic virus that replicates in the tumor cells and is inhibited from replicating in non-tumor cells; and wherein the lytic conditions comprise infective conditions, wherein the isolated oncolytic virus comprises an adenovirus not having a functional viral oncoprotein; and wherein tumor cells lack a functional p53- gene product **(claim 13)**,

wherein the functional viral oncoprotein comprises a p53- binding protein **(claim 14)**,

wherein the lytic agent comprises an isolated nucleic acid expression construct that encodes a gene comprising: a cytolytic gene **(claim 19)**.

It is noted that paragraph 0057 of the specification defines "stimulus" as being "any action or agent that causes or changes an activity in an organism, organ, cell, or part thereof", wherein "[I]n general, the stimulus described in specific embodiments are "in addition" to any change or impulse resulting from

the introduction of the lytic agent to the tumor cells". Thus, for examination purposes, the term "stimulus" is interpreted to encompass chemotherapeutic agents as such agents would be expected to cause or change an activity in a tumor cell.

US Patent No. 6,080,578 teaches methods and compositions for treating neoplastic conditions by viral-based therapy wherein mutant virus lacking viral proteins which bind and/or inactivate p53 are administered to a patient having a neoplasm which comprises cells lacking p53 function (abstract). US Patent No. 6,080,578 further teaches that the mutant virus is able to substantially produce a replication phenotype in neoplastic cells but is substantially unable to produce a replication phenotype in non-replicating, non-neoplastic cells having essentially normal p53 function (abstract). US Patent No. 6,080,578 further teaches that viral mutants lacking the capacity to express a functional p53 inactivating protein (e.g. adenovirus E1b p55) will manifest a replication phenotype in $p53^{(-)}$ cells (column 8, lines 27-31). US Patent No. 6,080,578 further teaches that wild-type adenovirus E1bp55 protein binds to p53 in infected cells and produce a substantial inactivation of p53 function (column 11, lines 25-28). US Patent No. 6,080,578 further teaches that one of the human neoplasms comprising cells that lack p53 function that may be treated with the adenoviral constructs of the invention is nasopharyngeal carcinoma. US Patent No. 6,080,578 further teaches that adenoviral therapy of the invention may be combined with other antineoplastic protocols, such as conventional chemotherapy. US Patent No. 6,080,578 further teaches that adenoviral therapy of the invention may incorporate the expression of a cytotoxic gene (abstract). US Patent No. 6,080,578 further teaches that adenoviral vectors having mutations in the E1B55 gene were derived from Ad5 (column 20, lines 15-64). Thus, all of the claim limitations are met.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by US Patent Publication No. US2002/0006914 (published Jan. 17, 2002).

The claims are drawn to the following:

a method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

US Patent Publication No.US2002/0006914 teaches a method for enhancing the effect of a cancer therapy by introducing wild-type therapy-sensitizing gene activity into tumor cells and subjecting the tumor cells to a cancer therapy such as chemotherapy, radiotherapy, or biological therapy, including immunotherapy, cryotherapy and hyperthermia (abstract). US Patent Publication No. US2002/0006914 further teaches that the cancers that can be treated include head and neck cancers (paragraph 0008). US Patent Publication No. US2002/0006914 further teaches that a therapy-sensitizing gene is a gene which may promote apoptosis (paragraph 0011). US Patent Publication No. US2002/0006914 further teaches that therapy sensitizing genes may be delivered by viral vectors, including adenovirus vectors (paragraph 0020). Thus, all of the claim limitations are met.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ries et al. (2002, January 7, Br. J. Cancer 86(1):5-11) in view of Yosef et al. (2001, Cancer Research 61:8361-8365).

A method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

wherein the stimulated tumor expresses at least one chaperone protein at an elevated level compared to that of the tumor prior to applying the stimulus and wherein the chaperone protein comprises a heat shock protein ("HSP") **(claim 27)**,

wherein the heat shock protein is HSP 70 **(claim 28)**.

It is noted that paragraph 0057 of the specification defines "stimulus" as being "any action or agent that causes or changes an activity in an organism, organ, cell, or part thereof", wherein "[I]n general, the stimulus described in specific embodiments are "in addition" to any change or impulse resulting from the introduction of the lytic agent to the tumor cells". Thus, for examination purposes, the term "stimulus" is interpreted to encompass chemotherapeutic agents as such agents would be expected to cause or change an activity in a tumor cell.

Ries et al. teaches as set forth above in Section 5 but does not specifically teach the following:

wherein the stimulated tumor expresses at least one chaperone protein at an elevated level compared to that of the tumor prior to applying the stimulus and wherein the chaperone protein comprises a heat shock protein ("HSP"), or wherein the heat shock protein is HSP 70.

Yosef et al. teaches that heat shock protein and heat shock protein 70 (inducible) enhance the oncolytic effect of replicative adenovirus (title). Yosef et al. also teaches the use of an adenoviral vector that has been modified to express an hsp70 protein.

It would have prima facie obvious for one of skill in the art to have combined the teaching of Ries on the use of oncolytic adenovirus with the teaching of Yosef on the enhancement oncolytic adenovirus effect with hsp70 expression to modify the adenoviral vector of Ries to contain an hsp70 gene for expression in transfected tumor cells because of the explicit teaching of enhanced oncolytic effect in Yosef. One of skill in the art would have had a

reasonable expectation of success because of the success demonstrated of enhanced oncolytic effect in Yosef.

14. Claims 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ries et al. (2002, January 7, Br. J. Cancer 86(1):5-11).

The claims are drawn to the following:

a method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor **(claim 4)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

wherein the first number of rounds is in a range of 1 to about 5 rounds **(claim 5)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

wherein the first period of time is about 1 to about 10 days **(claim 6)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

further comprising: applying an in vivo stimulus to the treated tumor for a second-number of rounds **(claim 7)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

further comprising: applying an in vivo stimulus to the treated tumor for a second-number of rounds, wherein the second-number of rounds is in a range of about 1 to about 16 rounds **(claim 8)**,

It is noted that paragraph 0057 of the specification defines "stimulus" as being "any action or agent that causes or changes an activity in an organism, organ, cell, or part thereof", wherein "[I]n general, the stimulus described in specific embodiments are "in addition" to any change or impulse resulting from the introduction of the lytic agent to the tumor cells". Thus, for examination purposes, the term "stimulus" is interpreted to encompass chemotherapeutic agents as such agents would be expected to cause or change an activity in a tumor cell.

Ries et al. teaches as set forth above in Section 5 but does not specifically teach the following:

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds:

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds in a range of 1 to about 5 rounds,

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds and further applying an in vivo stimulus to the treated tumor for a second-number of rounds,

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds and further applying an in vivo stimulus to the treated tumor for a second-number of rounds in the range of 1 to 16 rounds,

It would have prima facie obvious for one of skill in the art to employ conventional dosing regimens known in the art for the administration of the adenovirus of Ries in combination with chemotherapy to arrive at the claimed therapeutic regimens because such dosing regimens are conventional. Specifically, Ries teaches a multiple dose treatment schedule with the adenovirus and a multiple dose treatment schedule with cancer chemotherapy is well known in the art. Thus, the use of multiple dose treatment regimens would be routine in the art and the criticality of claimed therapeutic regimens are not recited in the instant specification or claims. One of skill in the art would have

had a reasonable expectation of success in employing such dosing regimens because of the success of the synergistic combination of the adenoviral therapy and chemotherapy taught in Ries.

15. Claims 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,080,578 (issued June 2, 2000) in view of Yosef et al. (2001, Cancer Research 61:8361-8365).

The claims are drawn to the following:

a method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1),**

wherein the stimulated tumor expresses at least one chaperone protein at an elevated level compared to that of the tumor prior to applying the stimulus and wherein the chaperone protein comprises a heat shock protein ("HSP") **(claim 27),**

wherein the heat shock protein is HSP 70 **(claim 28)**.

It is noted that paragraph 0057 of the specification defines "stimulus" as being "any action or agent that causes or changes an activity in an organism, organ, cell, or part thereof", wherein "[I]n general, the stimulus described in specific embodiments are "in addition" to any change or impulse resulting from the introduction of the lytic agent to the tumor cells". Thus, for examination purposes, the term "stimulus" is interpreted to encompass chemotherapeutic agents as such agents would be expected to cause or change an activity in a tumor cell.

US Patent No. 6,080,578 teaches as set forth above in Section 6 but does not specifically teach the following:

wherein the stimulated tumor expresses at least one chaperone protein at an elevated level compared to that of the tumor prior to applying the stimulus and wherein the chaperone protein comprises a heat shock protein ("HSP"), or wherein the heat shock protein is HSP 70.

Yosef et al. teaches that heat shock protein and heat shock protein 70 (inducible) enhance the oncolytic effect of replicative adenovirus (title). Yosef et al. also teaches the use of an adenoviral vector that has been modified to express an hsp70 protein.

It would have prima facie obvious for one of skill in the art to have combined the teaching of US Patent No. 6,080,578 on the use of oncolytic adenovirus with the teaching of Yosef on the enhancement oncolytic adenovirus effect with hsp70 expression to modify the adenoviral vector of US Patent No. 6,080,578 to contain an hsp70 gene for expression in transfected tumor cells because of the explicit teaching of enhanced oncolytic effect in Yosef. One of skill in the art would have had a reasonable expectation of success because of the success demonstrated of enhanced oncolytic effect in Yosef.

16. Claims 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,080,578 (issued June 2, 2000).

The claims are drawn to the following:

A method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor **(claim 4)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

wherein the first number of rounds is in a range of 1 to about 5 rounds **(claim 5)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

wherein the first period of time is about 1 to about 10 days **(claim 6)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

further comprising: applying an in vivo stimulus to the treated tumor for a second-number of rounds **(claim 7)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus,

further comprising: repeating following method steps for a first-number of rounds:

(a) contacting the tumor cells in the treated tumor with the lytic agent in vivo; waiting a period of time; and

(b) applying an in vivo stimulus to the treating tumor,

further comprising: applying an in vivo stimulus to the treated tumor for a second-number of rounds, wherein the second-number of rounds is in a range of about 1 to about 16 rounds **(claim 8)**,

US Patent No. 6,080,578 teaches as set forth above in Section 6 but does not specifically teach the following:

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds:

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds in a range of 1 to about 5 rounds,

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds and further applying an in vivo stimulus to the treated tumor for a second-number of rounds,

repeating the lytic agent and in vivo stimulus steps for a first-number of rounds and further applying an in vivo stimulus to the treated tumor for a second-number of rounds in the range of 1 to 16 rounds,

It would have prima facie obvious for one of skill in the art to employ conventional dosing regimens known in the art for the administration of the

adenovirus of US Patent No. 6,080,578 in combination with chemotherapy to arrive at the claimed therapeutic regimens because such dosing regimens are conventional. Specifically, multiple dose treatment schedules are known in the art. Thus, multiple dose treatment regimens would be routine in the art and the criticality of claimed therapeutic regimens are not recited in the instant specification or claims. One of skill in the art would have had a reasonable expectation of success in such dosing schemes because of the success of the synergistic combination of the adenoviral therapy and chemotherapy taught in US Patent No. 6,080,578.

17. Claims 2-3, 9, 10 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Publication No.US2002/0006914 in view of Qi et al. (2001, Int. J. Hyperthermia 17(1):38-47) (abstract only).

The claims are drawn to the following:

a method for ablating tumor cells in a subject having at least one tumor site, the method comprising:

(a) contacting the tumor cells in at least one tumor with a lytic agent in vivo, under lytic conditions, forming a treated tumor;

(b) applying a sufficient in vivo stimulus to the treated tumor forming a stimulated tumor **(claim 1)**,

wherein contacting the tumor cells with a lytic agent occurs before applying the in vivo stimulus **(claim 2)**,

further comprising: waiting a first period of time after contacting the tumor cells in at least one tumor with a lytic agent in vivo, but before applying the in vivo stimulus **(claim 3)**,

wherein applying stimulus is for about 15 minutes to about 90 minutes **(claim 9)**,

wherein the tumor comprises: a nasopharyngeal carcinoma **(claim 10)**,

wherein the in vivo stimulus comprises a local hyperthermia in a range of about 1 to about 7 degrees Celsius above a normal body temperature for the subject **(claim 20)**,

US Patent Publication No.US2002/0006914 teaches as set forth above in section 7, but does not teach the following:

contacting the tumor cells with a lytic agent before applying the in vivo stimulus,

waiting a first period of time after contacting the tumor cells with a lytic agent before applying the in vivo stimulus,

wherein the tumor comprises a nasopharyngeal carcinoma,

wherein the in vivo stimulus comprises a local hyperthermia in a range of about 1 to about 7 degrees Celsius above a normal body temperature for the subject.

Qi et al. teaches that the treatment of cells of a nasopharyngeal carcinoma cell line with an adenoviral vector carrying the p53 gene in combination with hyperthermia (HT) (43 degrees for two hours, wherein HT treatment was initiated 24 hours after infection with the viral vector) resulted in 70% of the cells displaying apoptosis after the combination of treatments. Hyperthermia treatment was for a range of 0-2 hours

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of US Patent Publication No. US2002/0006914 on the combination of an adenoviral vector carrying a p53 gene in combination with hyperthermia for the treatment of cancer with the specific teaching of Qi et al. that the treatment of nasopharyngeal cells with the combined treatment resulted in enhanced apoptotic effect to arrive at the claimed inventions cancer because of the explicit suggestion in Qi of the combination for use with nasopharygeal cancer cells, the administration of the viral vector prior to the hyperthermia treatment, and a hyperthermia temperature

in the claimed range. One of skill in the art would have had a reasonable expectation of success in making the combination because of the demonstrated efficacy in Qi of the combined viral and hyperthermia treatment.

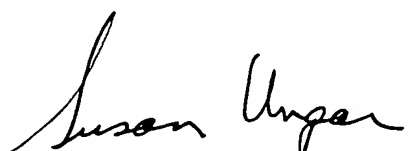
18. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



SUSAN UNGAR, PH.D
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